PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 22 December 2000 (22.12.00)	
International application No. PCT/NL00/00269	**Applicant's or agent's file reference** P49376PC00
International filing date (day/month/year) 26 April 2000 (26.04.00)	**Priority date** (day/month/year) 26 April 1999 (26.04.99)
Applicant VAN DER GREEF, Jan et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

21 November 2000 (21.11.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Juan Cruz
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

CERTIFICATE OF MAILING BY "EXPRESS MAIL" (37 CFR 1.10) Applicant(s): Jan van der Greef et al.			09/980647 Docket No. 101137-32
Serial No. TBA	Filing Date Concurrently Herewith	Examiner TBA	Group Art Unit TBA

Invention: **Mass Spectrometry-based Technologies for Continuous Flow Bioassays Using Known Ligands**

I hereby certify that the following correspondence:

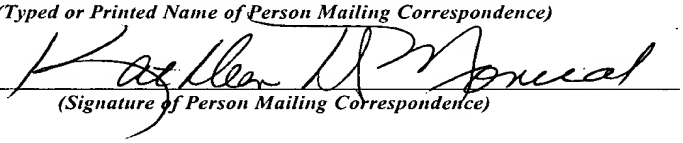
U.S.national stage application of PCT/NL00/00269

(Identify type of correspondence)

is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 in an envelope addressed to: The Assistant Commissioner for Patents, Washington, D.C. 20231 on

October 26, 2001
(Date)

Kathleen D. Monical
(Typed or Printed Name of Person Mailing Correspondence)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EE	Estonia	**LR**	Liberia	**SG**	Singapore		

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/NL 00/00269

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N33/566 G01N30/46

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MARTIN SEIFERT ET AL.: "a new concept for the bioeffects-related analysis of xenoestrogens: hyphenation of receptor assays with LC-MS" FRESNIUS JOURNAL OF ANALYTICAL CHEMISTRY, vol. 363, 1 April 1999 (1999-04-01), pages 767-770, XP002126676 Springer-Verlag page 769, column 2 -page 770, column 1, paragraph 2 --- -/--	1,3,4

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 June 2000	28/06/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Zinngrebe, U

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/NL 00/00269

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	E.S.M. LUTZ ET AL: "Applying hollow fibres for separating free and bound label in continuous-flow immunochemical detection" JOURNAL OF CHROMATOGRAPHY A., vol. 755, 1996, pages 179-187, XP004014703 ELSEVIER SCIENCE., NL ISSN: 0021-9673 page 180 page 181, column 2, last paragraph -page 182 * conclusions *	1,3,4
A	OOSTERKAMP A J ET AL: "Gradient reversed-phase liquid chromatography coupled on-line to receptor-affinity detection based on the urokinase receptor" JOURNAL OF CHROMATOGRAPHY B: BIOMEDICAL SCIENCES & APPLICATIONS,NL,ELSEVIER SCIENCE PUBLISHERS, vol. 715, no. 1, page 331-338 XP004147005 ISSN: 0378-4347 page 331, column 2, paragraph 2 -page 332, column 1, paragraph 2 page 333 page 336, column 2, paragraph 1	1
A	MICHAEL L. NEDVED ET AL.: "characterization of benzodiazepine "combinatorial" chemical libraries by on-line immunoaffinity extraction, coupled column HPLC-ion spray mass spectrometry-tandem mass spectrometry" ANALYTICAL CHEMISTRY., vol. 68, no. 23, 1 December 1996 (1996-12-01), pages 4228-4236, XP002117165 AMERICAN CHEMICAL SOCIETY. COLUMBUS., US ISSN: 0003-2700 abstract	1,2
A	YINLIANG F. HSIEH ET AL.: "multidimensional chromatography coupled with mass spectrometry for target-based screening" MOLECULAR DIVERSITY, vol. 2, 1996, pages 189-196, XP002117170 ESCOM cited in the application abstract	1,2

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INTERNATIONAL SEARCH REPORT

Inten nal Application No
PCT/NL 00/00269

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	KARL F. BLOM ET AL.: "determining affinity-selected ligands and estimating binding affinities by online size exclusion chromatography/liquid chromatography-mass spectrometry" JOURNAL OF COMBINATORIAL CHEMISTRY, vol. 1, 18 December 1998 (1998-12-18), pages 82-90, XP002117168 American Chemical Socieity page 82, column 2 -page 83, column 1, paragraph 1 * Conclusions *	1,2
A	GREGORY HUYER: "Affinity Selection from Peptide Libraries to determine substrate specifiy of protein tyrosine phosphatases" ANALYTICAL BIOCHEMISTRY, vol. 258, 1998, pages 19-30, XP002117169 Academic Press abstract	1,2

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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
P49376PC00		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/NL00/00269	26/04/2000	26/04/1999
International Patent Classification (IPC) or national classification and IPC G01N33/566		
Applicant SCREEN TEC B.V. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21/11/2000	18.07.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Vanmontfort, D Telephone No. +49 89 2399 8457

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/NL00/00269

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

   1-10 as originally filed

   Claims, No.:

   1-10 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-8
	No:	Claims	9, 10
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-10
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

1. S cti n V

Reference is made to the following documents:

D1 SEIFERT et al., FRESNIUS JOURNAL OF ANALYTICAL CHEMISTRY, vol. 363, 1 April 1999, pages 767-770

D2 LUTZ et al., JOURNAL OF CHROMATOGRAPHY A., vol. 755, 1996, pages 179-187

D3 GREGORY HUYER, ANALYTICAL BIOCHEMISTRY, vol. 258, 1998, pages 19-30.

D4 NEDVED et al., ANALYTICAL CHEMISTRY., vol. 68, no. 23, 1 December 1996, pages 4228-4236.

D5 YINLIANG F. HSIEH et al., MOLECULAR DIVERSITY, vol. 2, 1996, pages 189-196. ESCOM cited in the application

D6 BLOM et al., JOURNAL OF COMBINATORIAL CHEMISTRY, vol. 1, 18 December 1998 (1998-12-18), pages 82-90.

1.1 The arguments put forward by the Applicant in their letter of 02.04.01, in reply to the written opinion dated 21.12.00, have been taken into consideration. However, it is still considered that the subject-matter of claim 1 does not meet the requirements of Article 33(3) PCT.

D2, which is considered to represent the most relevant state of the art, discloses an on-line chromatography-immunochemical detection method comprising:

1) adding unlabelled antibodies (affinity molecule) to the LC effluent and allowing to react with analytes eluting from the LC column
2) adding a labelled ligand to the reaction mixture
3) separation of free and bound ligands by restricted access column or by hollow fibre module
4) immunochemical detection.

The subject-matter of claim 1 differs in that the detection is done by a mass spectrometer (MS). The problem to be solved by the present invention may therefore be regarded as the provision of an improved on-line detection method which does not require the use of labelled ligands. There is an indication in D1 (page 770, left column, second paragraph and Figure 6) that the most advanced technology is seen in **label-fr e** homogenous binding assays followed by the

separation of free ligands and ligand-receptor complexes by means of HPLC-MS. The fact that the effluent in D1 is obtained from a solid support or batch based process is not relevant because the present claim does only specify the steps after obtaining the effluent.
Furthermore, D3-D6 disclose screening methods using chromatography coupled with mass spectrometry. Therefore, it would be obvious for a person skilled in the art to use mass spectrometry in the method of D2 in order to solve the problem posed. Hence, the subject-matter of claim 1 does not involve an inventive step (Article 33(3) PCT). The same applies to dependent claims 2-6.

1.2 Dependent claims 7 and 8 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step (Article 33(3) PCT). These features are merely straightforward possibilities from which the person skilled in the field of mass spectrometry would select, in accordance with circumstances, without the exercise of inventive skill. Furthermore, D5 (page 191, Materials and Methods) and D3 (page 21 lines 20-22) mention the use of an electrospray ionization mass spectrometer in on-line detection methods.

1.3 The subject-matter of claim 9 is not novel (Article 33(2) PCT).
A compound detected by the method of claims 1-8 includes any compound which binds to the added affinity molecule. In the description (page 9 line 25-30) of the present application is disclosed that said affinity molecule includes estrogen receptors, glucocorticoid receptors, ... Since the detected compound will therefore be estrogen or glucocorticoid, ... and these compounds are known compounds, the subject-matter of claim 9 is not novel.
Furthermore, for the assessment of claims of products defined in terms of a process, no unified criteria exist in the PCT Contracting States. For the EPO, for example, a product is not rendered novel merely by the fact that it is detected by means of a new process how difficult or time-consuming the technology may be. Claims for products defined in terms of a process of manufacture are admissible only if the products as such fulfil the requirements of patentability, i.e. that they are novel and inventive.

1.4 The subject-matter of claim 10 is not novel (Article 33(2) PCT).
The use of said detected compound such as estrogen, glucocorticoid,... as a ligand for affinity molecules (see also point 1.3) is general laboratory practice in the field of immunological methodology.

2. Section VII

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in D2 is not mentioned in the description, nor is this document identified therein.

3. Section VIII

The application does not meet the requirements of Rule 5.1(a)(v) PCT because the description does not give any example for carrying out the invention claimed. The description only describes the methodology in theory without giving any working example of the claimed on-line detection method.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
P49376PC00		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/NL 00/ 00269	26/04/2000	26/04/1999
Applicant		
SCREEN TEC B.V. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

   [X] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/NL 00/00269

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N33/566 G01N30/46

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	MARTIN SEIFERT ET AL.: "a new concept for the bioeffects-related analysis of xenoestrogens: hyphenation of receptor assays with LC-MS" FRESNIUS JOURNAL OF ANALYTICAL CHEMISTRY, vol. 363, 1 April 1999 (1999-04-01), pages 767-770, XP002126676 Springer-Verlag page 769, column 2 -page 770, column 1, paragraph 2 --- -/--	1,3,4

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 June 2000	28/06/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Zinngrebe, U

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	E.S.M. LUTZ ET AL: "Applying hollow fibres for separating free and bound label in continuous-flow immunochemical detection" JOURNAL OF CHROMATOGRAPHY A., vol. 755, 1996, pages 179-187, XP004014703 ELSEVIER SCIENCE., NL ISSN: 0021-9673 page 180 page 181, column 2, last paragraph -page 182 * conclusions *	1,3,4
A	OOSTERKAMP A J ET AL: "Gradient reversed-phase liquid chromatography coupled on-line to receptor-affinity detection based on the urokinase receptor" JOURNAL OF CHROMATOGRAPHY B: BIOMEDICAL SCIENCES & APPLICATIONS,NL,ELSEVIER SCIENCE PUBLISHERS, vol. 715, no. 1, page 331-338 XP004147005 ISSN: 0378-4347 page 331, column 2, paragraph 2 -page 332, column 1, paragraph 2 page 333 page 336, column 2, paragraph 1	1
A	MICHAEL L. NEDVED ET AL.: "characterization of benzodiazepine "combinatorial" chemical libraries by on-line immunoaffinity extraction, coupled column HPLC-ion spray mass spectrometry-tandem mass spectrometry" ANALYTICAL CHEMISTRY., vol. 68, no. 23, 1 December 1996 (1996-12-01), pages 4228-4236, XP002117165 AMERICAN CHEMICAL SOCIETY. COLUMBUS., US ISSN: 0003-2700 abstract	1,2
A	YINLIANG F. HSIEH ET AL.: "multidimensional chromatography coupled with mass spectrometry for target-based screening" MOLECULAR DIVERSITY, vol. 2, 1996, pages 189-196, XP002117170 ESCOM cited in the application abstract	1,2

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1

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	KARL F. BLOM ET AL.: "determining affinity-selected ligands and estimating binding affinities by online size exclusion chromatography/liquid chromatography-mass spectrometry" JOURNAL OF COMBINATORIAL CHEMISTRY, vol. 1, 18 December 1998 (1998-12-18), pages 82-90, XP002117168 American Chemical Socieity page 82, column 2 -page 83, column 1, paragraph 1 * Conclusions *	1,2
A	GREGORY HUYER: "Affinity Selection from Peptide Libraries to determine substrate specifiy of protein tyrosine phosphatases" ANALYTICAL BIOCHEMISTRY, vol. 258, 1998, pages 19-30, XP002117169 Academic Press abstract	1,2

1